REMARKS

This amendment is submitted in an earnest effort to bring this case to issue without delay.

Applicants wish to reiterate their claim to the benefit of their Hungarian priority date of 7 July 1999 pursuant to the International Convention. A certified copy of Hungarian Patent Application P99021 filed 7 July 1999 has already been made of record as part of Applicants' PCT/HU00/00074 filed 4 July 2000 of which the instant application is the U.S. National Phase. The Examiner has already acknowledged Applicants' perfected right of priority.

Applicants have canceled claims 1 through 27 and added new claims 28 through 54. Antecedent basis for the new claims may be found in the specification on pages 4 through 23 and in the specific examples. Thus claims 28 through 54 are now in the application and are presented for examination.

Applicants have amended the first page of the specification to state as follows:

CROSS REFERENCE TO RELATED APPLICATION

This application is a 371 of PCT/HU00/00074 filed 4 July 2000.

The PCT Transmittal Document made of record on

21 March 2002 made reference to both the International filing date of 4 July 2000 for PCT/HU00/00074 and the claim to the benefit of the priority date of Applicants' Hungarian Patent Application filed 7 July 1999. Thus there should be no need to file a petition to gain entry of the Cross Reference into the specification.

Applicants will in the near future submit a substitute specification to remove a number of inconsistencies and informalities in the original application.

Applicants have presented new claims 28 through 54 taking into consideration the bases for rejection of original claims 1 through 27 under 35 USC 112, second paragraph as set forth in Section 3 of the office action. Applicants have chosen to submit new clean claims, rather than attempt to amend the original claims by strike-out and underline since the original claims all involve chemical formulae and it is believed that attempting to use the strike-out and underline method of amendment will create a good deal of confusion as to the claims cover. It is believed that all claims now presented are clear and definite and in full compliance with the requirements of that section of the statute. Applicants specifically note that they have included throughout the claims within the definition of R^1 the moiety $-CO-NR^5R^6$ instead of the moiety $-NR^5R^6$. Inclusion of $-NR^5R^6$ instead of $-CO-NR^5R^6$ within the definition of R^1 was an obvious error since there are no compounds of the Formula (I) in the present application where R^1 includes -

NR^5R^6. Furthermore the species of Examples 14 through 17 provide obvious antecedent basis for compounds of the Formula (I) with a carbamoyl or substituted-carbamoyl substituent in the 8-position of the benzodiazepine nucleus. See new compound claims 28 through 31 covering the compounds of the Formula (I) and the narrower subgeneric compounds of the Formulae (IA), (IB) and (IC) as well as the new pharmaceutical composition claims 47, 49, 51 and 53. Furthermore new process to prepare the Formula (I) compound claim 42 not only includes the moiety $-CO-NR^5R^6$ within the definition of R^1 in Formula (I), but also includes within process variant (d), the compound of the Formula (VI) used to prepare the new Formula (I) compounds. Consistent with the correction of the definition of R^1 in structural Formula (I) the corresponding correction in the structure of Formula (VI) has been corrected as well to show that the substituent bonded to the 8-position of the benzodiazepine nucleus is $-CO-NR^5R^6$ and not $-CONR^7$ R^8 which is a substituent within the scope of moiety R^3 bonded to the heterocyclic nitrogen atom in the 7-position of the benzodiazepine nucleus in the compounds of the Formula (I).

Applicants have responded to the Examiner's rejection of original claims 16 through 27 under 35 USC 112, first paragraph as set forth in Section 2 of the office action by canceling all of these claims and submitting in place of those claims new claims 45 through 54. The new claims are believed to be in full compliance

with the first paragraph of 35 USC 112 since all of these claims are based upon a specification that will enable those "skilled in the art" to practice the invention as it is now claimed without the need to conduct undue experimentation.

It is noted that claims 25 and 26 directed respectively to the preparation of a pharmaceutical composition by mixing a compound of the Formula (I) and a carrier and to the use of a compound of the Formula (I) to treat a number of neurodegenerative disorders have been canceled without replacement. Cancellation of claim 26 without replacement also obviates the rejection of that claim set forth under 35 USC 101 as non-statutory.

New claims 47 through 54 include independent pharmaceutical composition claims 47, 49, 51 and 53. All of the claims include the same Formula (I) compounds as the active ingredient. However, each of these claims is directed to a pharmaceutical composition whose utility expressed in the preamble of the claim is not identical. In the preamble of claim 49, it is stated that the pharmaceutical compositions are useful for the treatment of epilepsy. In the case of pharmaceutical compositions for treating epilepsy the Examiner indicated at the bottom of page 3 of the office action that she believed that this aspect of the invention was enabled by the specification. Thus at the outset no rejection of pharmaceutical composition 49 should be given under 35 USC 112, first paragraph.

Pharmaceutical composition claim 53 broadly defines the purpose of the pharmaceutical composition as "a pharmaceutical composition for treating a neurodegenerative disease...". Applicants believe that this broad definition of the disease to be treated is supported in the specification as well. The Examiner has questioned whether the presently claimed compounds of the Formula (I) would be effective in treating a number of well known neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, Huntington's disease and ALS. The Examiner points out that many of these diseases are intractable and that there is no known treatment, let alone a cure, for many of these diseases. Furthermore even though all of these diseases are neurodegenerative diseases, the origins of these respective diseases may be entirely different. Thus the Examiner has indicated that defining the diseases to be treated in the pharmaceutical composition claims as "neurodegenerative diseases" is beyond the scope of the anabling disclosure provided by the specification.

Applicants ask that the Examiner reconsider this rejection with regard to new pharmaceutical composition claim 53. Applicants are submitting herewith a Declaration Under 37 CFR 1.132 of Zoltan Greff which provides both background information and physiological test data to establish that several represent compounds of the present Formula (I) have activity that enables their use to treat a number of neurodegenerative disorders including

global cerebral ischaemia, amyotropic lateral sclerosis, stroke, and cystic periventricular leukomalacia. Applicants disclose on pages 22 and 23 of the present application that the presently claimed compounds of the Formula (I) are effective to treat neurodegenerative diseases in view of their ability to antagonize AMPA/cainate receptors. There are a good deal of literature references as is evidenced by the Greff declaration of the connection between this activity and the treatment of neurodegenerative diseases. The physiological data included in the declaration underscores the connection between the presently claimed compounds, the antagonization of AMPA/cainate receptors, and the practical effective treatment of a neurodegenerative disease. Thus it is believed that claim 53 should not be rejected under 35 USC 112, first paragraph, as based upon a non-enabling disclosure.

Alternatively to claim 53 the Examiner is asked to consider claim 47. Claim 47 is directed to a pharmaceutical composition used for "antagonizing a non-competitive AMPA/cainate receptor" rather than reciting any specific disease. See pages 22 and 23 of the specification near the top for antecedent basis. Thus in claim 47 Applicants have not committed to the effective treatment of any particular neurodegenerative disorder, but have committed to the underlying activity of "antagonizing a non-competitive AMPA/cainate receptor."

Applicants believe that reciting this general activity, rather than a list of specific diseases, is an alternative to claim the pharmaceutical compositions according to the present invention may be more acceptable to the Examiner than recitation of specific neurodegenerative disorders.

Claim 51 is the last of the four independent pharmaceutical composition claims. This claim recites some specific neurodegenerative disorders that are amenable to treatment with a new compound of the Formula (I). These specific disorders include stroke, Parkinson's disease, multiple sclerosis, and amyotropic lateral sclerosis. It is believed that the reference and the data in the Declaration Under 37 CFR 1.132 provide sufficient data to establish that the treatment of these diseases with Applicants' new Formula (I) compounds overcome the basis for the Examiner's rejection of the original pharmaceutical claims under 35 USC 112, first paragraph.

For the same reasons that the composition claims 47, 49,51 and 53 are believed to be in full compliance with the requirements of 35 USC 112, it is believed that method of treatment claims 48, 50, 52 and 54 should be in full compliance with this section of the statute as well. Each of these method of treatment claims recites the same pharmaceutical utility or activity as is recited in the immediately preceding pharmaceutical composition claim.

The Examiner has rejected claims 1, 2, 4, 5, 10 through 13, 16, 17 and 22 through 27 as obvious under 35 USC 103 citing U.S. Patent 5,756,495 to HAMORI et al. The Examiner argues that many of the compounds falling within the scope of generic claim 1 are structurally very similar to the compounds disclosed in HAMORI et al except for the fact that the benzene ring in Applicants' compounds contains a methyl group ortho to the amino or nitro substituent whereas the reference compounds contain only a hydrogen instead of a methyl group. Nonetheless the Examiner considers the structures of the prior art compounds and many of the presently claimed compounds as very similar and believes that she has established a basis for prima facie structural obviousness for many of the presently claimed compounds.

The Examiner has not included claims 3, 6 through 9, 14, 15, and 18 through 21 in the rejection. All of these claims, with the exception of claims 14 and 15, are directed to the Formula (IB) compounds and to pharmaceutical compositions containing these compounds. Thus the Examiner has not applied U.S. Patent 5,756,495 against any of the Applicants' original claims directed solely to the new Formula (IB) compounds, a sub-group of the Formula (I) compounds because the Formula (IB) compounds are directed to 7,8-dihydro-8-methyl-2H-1,3-dioxolo[4,5-h][2,3]benzodiazepins having a 3-methyl substituent and either a 4-nitro or 4-amino substituent whereas the reference compounds have a

carbon-carbon double bond between either the 7- and 8-positions (Formula II) or the 8- and 9-positions (Formula I).

Applicants have canceled all claims originally presented and have submitted new claims 28 through 54. New claims 30, 33, 35, 36 and 37 are all directed to the new Formula (IB) compounds and so are believed at the outset to be in condition for allowance.

The Examiner has perhaps established a prima facie basis for the structural obviousness of the presently claimed compounds of the Formula IC. While the broad generic definition of the compounds of the Formula (I) according to HAMORI et al with its floating substituents R^1 and R^2 on the benzene ring is broad enough to encompass the present Formula (IC) compounds, there is no disclosure in this reference of any species having a methyl substituent and either a nitro or amino substituent ortho to one another. Thus Applicants' compounds of the Formula (IC) constitute a selective invention within the scope of the HAMORI et al compounds. The prima facie structural obviousness of the compounds of the Formula (IC) is rebutable by a showing of surprising or unobvious properties of the new Formula (IC) compounds over those of the prior art. In the present case Applicants have comparative data between several of their new Formula (IC) compounds where R^2 is amino and there is a methyl substituent ortho to the amino group over the corresponding prior art compounds where there is no methyl substituent ortho to the amino group. See Examples 35 and 36 of

the present application and the directly comparative data over the prior art compounds having no methyl substituent ortho to the amino group on page 30 of the present application. Note the data on page 30 showing longer-lasting activity when Applicants' compound of Example 35 is directly compared against the compound of Example 2 of U.S. Patent 5,756,495 and when Applicants' compound of Example 36 is directly compared against the compound of Example 45 of the patent. Thus any basis for the prima facie structural obviousness of the new compounds of the Formula (IC) has been rebutted by directly comparative data. Accordingly claims 31, 34, 38 and 39 are believed to be patentable over U.S. Patent 5,756,495.

Now Applicants turn to the compounds of the Formula (IA) as covered in claims 29, 32, 40 and 41. These claims are directed to 9H-1,3-dioxolo-[4,5-H][2,3}benzodiazepines with double bonds between both the 5,6- and the 7,8-positions of the nucleus. The structurally closest compounds appearing in U.S. Patent 5,756,495 are the compounds disclosed therein as the Formula (II) compounds. See col. 4 of the reference. These compounds are disclosed as starting materials with no indication that these compounds have any per se activity. The fact that the reference Formula (II) compounds may be used to make Formula (I) compounds with per se activity does not mean that the Formula (II) compounds would be expected to possess any activity per se.

Claims 40 and 41 are especially believed to be patentable over the cited prior art. The subgenus of claim 40 and the species of claim 41 are each limited to compounds with an 8-position substituent that is structurally far removed from the optionally substituted alkyl substituent R^4 in the corresponding position of the HAMORI et al Formula (II) compounds. Claim 41 is a species claim with a semicarbazono-methyl substituent in the 8-position, namely, $-CH=NNHCONH_2$, and there is no similar substituent bonded to the nucleus of the Formula (II) compounds disclosed in U.S. Patent 5,756,495. Furthermore in the test data set forth in the accompanying Declaration Under 37 CFR 1.132 of Zoltan Greff it is indicated that the compound of claim 41 has ben found to decrease cerebral infarct size in the tests concerning the activity of the new compounds against stroke. Note that the species of claim 41 is the species of Example 34 in the present application.

Applicants now have the following direct comments regarding the patentability of all of the new compounds of the Formula (I) over the prior art compounds of U.S. Patent 5,756,495.

The Examiner states that compounds according to the present invention are obvious in view of US 5,756,495 (Hamori et al.). We agree to the Examiner with respect that substituent definition in the compounds of the present invention and that of the Hamori patent are overlapping. However, we draw the attention of the Examiner to the following facts which prove that the com-

pounds according to our invention possess special structural characteristics, which distinctly delimit said compounds from those disclosed in HAMORI et at. and provide basis for the patentability of said compounds:

(a) The surprising feature of the compounds according to the invention is that 5-[4-amino-3-methyl-phenyl] substituted 1,3-dioxolo[4,5-h][2,3]benzodiazepines exhibit superior pharmacological effect with longer duration than analogues which do not have the methyl group in the ortho-position to the amino group in the 5-[4-amino-3-methyl-phenyl] substituent.

This phenomenon is demonstrated in the description by comparing the neuroprotective effect in magnesium chloride induced global cerebral ischaemia model of the compounds according to the present invention with those analogues which have a hydrogen atom instead of a methyl substituent in the ortho position to the amino group. This effect could not have been foreseen from the literature data. e.g. Hamori et al.

Furthermore, it is also demonstrated in tissue culture of liver cells in vitro that metabolic rate in the compounds according to the present invention is much slower with regard to the acetylation of the amino group of the 5-[4-amino-3-methyl-phenyl] substituent than in those which do not bear an o-methyl substituent relative to the amino group. Since N-acetylation is one main

metabolic route of the aromatic amino-group (see e.g. metabolism of sulfonamide antibiotics), from this observation it could be concluded that the elimination rate of the compounds bearing an o-methyl group is significantly lower than for those analogues where there is a hydrogen atom in the ortho position. Thus, the interval when the pharmaceutical effect exists is prolonged; therefore lower doses are to be administered and the administration period could be longer. Such properties are preferable both from pharmacological and toxicological points of view.

Human population is grouped into slow or rapid acetylators according to the rate of the metabolic N-acetylation reaction. Differences in this reaction rate are undesirable, since administration of the drug to a subject having slow acetylator phenotype may result in increased toxicity, as it has been demonstrated for a group of drugs, such as isoniazide or benzodiazepines. This risk is significantly decreased in the case of the compounds of the present invention, since the acetylation reaction rate is significantly decreased [A. Rane (1999). Phenotyping of drug metabolism n infants and children: potentials and problems. Pediatrics 104, 640-643].

In a different aspect, these advantages are to the benefit of the patient as well who has to ingest medication in prescribed intervals. The smaller the size of the medication and the longer the administration period, the greater is the willing-

ness of the patient to ingest said medication. Thus, patient compliance is also positively impaired.

In summary, compounds according to the present invention have surprisingly advantageous pharmacokinetic and metabolic properties which result in preferable pharmacological and toxicological profiles as well as increased patient compliance.

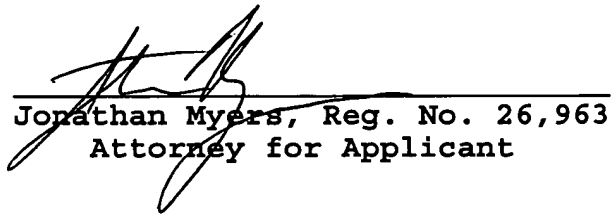
(b) The Hamori patent does not disclose specifically compounds which have a 4-amino-3-methyl-phenyl substituent on carbon in 5-position of the 1,3-dioxolo[4,5-h][2,3]benzodiazepine (or 1-position of the 2,3-benzodiazepine) ring structure. Neither intermediates bearing a 4-nitro-3-methylphenyl substituent in 5-position are contemplated. Furthermore, there is no mention of compounds which have any kind of substituent in the ortho position relative to the 4-aminophenyl or 4-nitrophenyl substituent in the 5-position. The only compound having substitution in position 3 and 4 of said phenyl ring is that of example 16, where the 5-substituent of the 1,3-benzo[4,5-h](2,3)diazepine structure is 4-methoxy-3-fluorophenyl. However, compounds with such substituents exhibit different pharmaceutical effects, such as spontaneous motor activity inhibiting, analgetic and narcosis potentiating effects and lack neuroprotective activity (e.g. compounds disclosed in DE 3 209 100), which are not desirable in the present patent application.

For the above reasons we believe that all of the new Formula (I) compounds covered in claims 28 through 41, compositions containing the new Formula (I) compounds in claims 47, 49, 51 and 53 and methods of treatment employing the new compounds in claims 48, 50, 52 and 54 are patentable over HAMORI et al, since a safer, longer-lasting, highly efficient medication is provided.

Lastly Applicants would like to discuss claims 42 through 46 directed to a process for preparing the new compounds of the Formula (I). These claims were submitted to replace claims 12 through 15. Applicants note that the Examiner has not rejected claims 14 and 15 pursuant to either 35 USC 112, second paragraph or 35 USC 103. New independent process claim 46 has been submitted to replace claims 14 and 15 and to focus specifically on this aspect of the process, namely, the reduction of the compounds of the Formula (I) where R^2 is nitro to obtain the compounds of the Formula (I) where R^2 is amino. Thus claim 46 is believed to be allowable at the outset. Furthermore since claims 42 through 45 are directed to a process to prepare the new compound s of the Formula (I) which are all believed to be patentable over the cited prior art, it is believed that a process to prepare these new compounds should be patentable as well.

Applicants believe that all claims now presented are allowable and a response to that effect is earnestly solicited. Applicants are enclosing a petition to obtain a one month extension of the term for response and a authorization to pay for the extension using the credit card of the undersigned attorneys.

Respectfully submitted,
The Firm of Karl F. Ross P.C.



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Enclosures: Declaration
Extension Petition
PTO 2038